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=> s HERG
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=> s l1 (3a) (mutat? or alterat? or insert? or delet? or substitu?)
L2       541 L1 (3A) (MUTAT? OR ALTERAT? OR INSERT? OR DELET? OR
SUBSTITU?)

=> s l2 and LQT
L3       67 L2 AND LQT

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L4       36 DUP REM L3 (31 DUPLICATES REMOVED)

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L4  ANSWER 1 OF 36  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
    reserved on STN                          DUPLICATE 1
AN  2006139070  EMBASE
TI  Modelling and imaging cardiac repolarization abnormalities.
AU  Rudy Y.
CS  Dr. Y. Rudy, Washington University in St. Louis, Cardiac Bioelectricity
    Center, 290 Whitaker Hall, St Louis, MO 63130-4899, United States.
    rudy@wustl.edu
SO  Journal of Internal Medicine, (2006) Vol. 259, No. 1, pp. 91-106. .
    Refs: 47
    ISSN: 0954-6820 E-ISSN: 1365-2796  CODEN: JINMEO
CY  United Kingdom
DT  Journal; Conference Article
FS  006    Internal Medicine
    014    Radiology
    018    Cardiovascular Diseases and Cardiovascular Surgery
    027    Biophysics, Bioengineering and Medical Instrumentation
LA  English
SL  English
ED  Entered STN: 11 Apr 2006
    Last Updated on STN: 11 Apr 2006
AB  Repolarization abnormalities, including those induced by the congenital or
    acquired long QT ( ***LQT*** ) syndrome, provide a substrate for
    life-threatening cardiac arrhythmias. In this article, we use
    computational biology to link ***HERG*** ***mutations***
    mechanistically to the resulting abnormalities of the whole-cell action
    potential. We study how the kinetic properties of I(Ks) (the slow delayed
    rectifier) that are conferred by molecular subunit interactions,
    facilitate its role in repolarization and 'repolarization reserve'. A new
    noninvasive imaging modality (electrocardiographic imaging) is shown to
    image cardiac repolarization on the epicardial surface, suggesting its
    possible role in risk stratification, diagnosis and treatment of
    ***LQT*** syndrome. .COPYRGT. 2005 Blackwell Publishing Ltd.

L4  ANSWER 2 OF 36  CAPLUS  COPYRIGHT 2006 ACS on STN
AN  2005:1019605  CAPLUS
DN  144:105520
TI  A novel splice ***mutation*** of ***HERG*** in a Chinese family
    with long QT syndrome
AU  Shang, Yun-peng; Xie, Xu-dong; Wang, Xing-xiang; Chen, Jun-zhu; Zhu,
    Jian-hua; Tao, Qian-min; Zheng, Liang-rong
CS  Department of Cardiovascular Diseases, First Affiliated Hospital, School
    of Medicine, Zhejiang University, Hangzhou, 310003, Peop. Rep. China
SO  Journal of Zhejiang University, Science, B (2005), 6B(7), 626-630
    CODEN: JZUSAM
PB  Zhejiang University Press
DT  Journal
LA  English
AB  Congenital long QT syndrome (LQTS) is a genetically heterogeneous disease
    in which six ion-channel genes have been identified. The
    phenotype-genotype relationships of the HERG (human ether-a-go-go-related
    gene) mutations are not fully understood. The objective of this study is
    to identify the underlying genetic basis of a Chinese family with LQTS and
    to characterize the clin. manifestations properties of the mutation.
    Single strand conformation polymorphism (SSCP) analyses were conducted on
    DNA fragments amplified by polymerase chain reaction from five ***LQT***
    -related genes. Aberrant conformers were analyzed by DNA sequencing. A
    novel splice mutation in C-terminus of HERG was identified in this Chinese
    LQTS family, leading to the deletion of 11-bp at the acceptor splice site
    of Exon9 [Exon9 IVS del (-12.fwdarw.-2)]. The mutation might affect,
    through deficient splicing, the putative cyclic nucleotide binding domain
    (CNBD) of the HERG K+ channel. This mutation resulted in a mildly
    affected phenotype. Only the proband had a history of syncopes, while the
    other three individuals with long QT interval had no symptoms. Two other
    mutation carriers displayed normal phenotype. No sudden death occurred in
    the family. The 4 affected individuals and the two silent mutation
    carriers were all heterozygous for the mutation. It is the first splice
    ***mutation*** of ***HERG*** reported in Chinese LQTS families.
    Clin. data suggest that the CNBD mutation may be less malignant than
    mutations occurring in the pore region and be partially dominant over
    wild-type function.
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RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L4 ANSWER 3 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2004:172928 BIOSIS
DN PREV200400174045
TI Gating and drug binding properties of A653-HERG, a highly conserved residue in K+ channels.
AU Stepanovic, Svetlana Z. [Reprint Author]; Petersen, Christina I. [Reprint Author]; Balser, Jeffrey R. [Reprint Author]
CS Anesthesiology, Vanderbilt University, Nashville, TN, USA
SO Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 522a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004. Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
AB HERG encodes a K+ channel involved in repolarization of the cardiac action potential. Congenital ***mutations*** in ***HERG*** that reduce delayed rectifier (IKr) current, and direct block of IKr by various pharmacological agents, evoke the long QT (***LQT***) syndrome, a condition that can lead to life-threatening arrhythmias. We studied mutations of an alanine residue, HERG-653A, conserved in all K+ channels. This alanine is located 5 residues downstream of the 'glycine hinge' implicated in K+ channel opening, and is near the 652Y and 656F residues implicated in drug binding to HERG. Mutant channels were expressed in Xenopus oocytes for analyzing gating and drug binding properties. Threonine(T), valine(V) and tyrosine(Y) substitutions evoked marked (gtoreq-50mV) hyperpolarization shifts in the voltage-dependence of activation (V1/2). For WT-HERG V1/2 was -26+-1.4 mV versus -83+-1.3, -76+-1.2, -85+-1.4 for T, V, Y, respectively (p<0.001). Cysteine(C), isoleucine(I), glycine(G) and serine(S) exhibited WT-like gating, with modest (<-25mV) shifts in V1/2 compared to WT-HERG. All mutants further hyperpolarized oocyte resting potential compared to WT-HERG. Inactivation gating and reversal potentials were not significantly altered in any of the 7 mutants. Mutants with large negative shift in V1/2 were constitutively open at all potentials, except for the inactivation gating, and did not display typical deactivation 'tail' currents. These mutants exhibit large inward current at membrane potentials below Erev (-82 mV). While alanine substitution disrupted dofetilide binding, as expected for an S6 mutation, these effects were greatest in T, Y, G (5-20% block versus 75% block for WT-HERG in 1 muM dofetilide) suggesting that the gating effects of A653 are not closely linked to the drug receptor properties. Our study reveals the importance of a conserved residue in K+ channels, which destabilizes the closed state, as reported in CNG1 channel.

L4 ANSWER 4 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2004:124224 BIOSIS
DN PREV200400127158
TI Truncation mutation P872fs877 in the C-terminus of the hERG potassium channel causes ***LQT*** by trafficking problems of heterotetrameric channels.
AU Raes, Adam L. [Reprint Author]; Paulussen, Aimee D. C.; Aerssens, Jeroen; Snyders, Dirk J. [Reprint Author]
CS Biomedical Sciences, University of Antwerp, Antwerp, Belgium
SO Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 279a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004. Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB ***Mutations*** in the KCNH2 (***hERG***) gene are responsible for the long QT syndrome (LQTS) by alterations of the delayed rectifier current IKr, thus delaying cardiac repolarization and rendering patients vulnerable to ventricular arrhythmias and sudden death. We identified and characterized a mutation (P872fs877) in the C-terminus of the KCNH2 gene in a large Dutch LQTS family. The mutation leads to a premature stop codon causing a C-terminal truncation of the protein. Biochemical and confocal microscopy techniques were used to investigate protein expression and trafficking. The biophysical properties of hERG channels were assayed by electrophysiological methods. The P872fs877 protein was clearly present in the membrane as determined by confocal microscopy. Homotetrameric expression of P872fs877 channels produced currents with minor changes in the biophysical properties and with only a small reduction in amplitude compared to WT. During voltage clamp experiments with action potential waveforms no significant differences were observed between WT and P872fs877. However, upon co-expression of WT and P872fs877
subunits, the fraction of hERG channels generating the current during action potential clamp experiments increased from apprx30% for WT and mutant to 70% for the heterotetramers. As a consequence, this increased repolarizing power during the action potential, only observed with heterotetramers of this C-terminal ***hERG*** ***mutation*** and WT subunits, should shorten the QT intervals. However, confocal microscopy revealed that the heterotetramers were largely retained in the ER. This dominant negative effect appears to predominate over the apparent increase in repolarizing power, thus explaining the LQTS phenotype.

L4 ANSWER 5 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 2004140112 EMBASE
TI Clinical and electrophysiological characterization of a novel ***mutation*** R863X in ***HERG*** C-terminus associated with long QT syndrome.
AU Teng S.; Ma L.; Dong Y.; Lin C.; Ye J.; Bahring R.; Vardanyan V.; Yang Y.; Lin Z.; Pongs O.; Hui R.
CS R. Hui, Sino-Ger. Lab. for Molec. Medicine, Fuwai Hospital, Peking Union Medical College, 167 Beilishilu, 100037 Beijing, China. huirutai@sglab.org
SO Journal of Molecular Medicine, (2004) Vol. 82, No. 3, pp. 189-196. .
Refs: 29
ISSN: 0946-2716 CODEN: JMLME8
CY Germany
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 12 Apr 2004
Last Updated on STN: 12 Apr 2004
AB We have found a novel nonsense mutation in the C-terminus of HERG in a four-generation Chinese family with long QT syndrome and investigated the molecular mechanism of this mutation in vitro. Six family members, including the proband, were clinically affected. Syncope and ventricular tachycardia of torsades de pointes were triggered by startling or emotional stress, and .beta.-adrenergic blockade treatment was ineffective. Haplotype analysis showed that only ***LQT*** (2) markers cosegregated with the disease, and sequence analysis revealed a substitution of T with C at nucleotide position 2770 of the HERG gene (U04270), which creates a stop codon at amino acid position 863 (R863X) of the HERG protein, leading to a deletion of 296 amino acids. Whole cell patch clamp studies showed that the R863X HERG could not induce time-dependent current. Coexpression of R863X with wild-type HERG showed reduced current densities and accelerated voltage-dependent inactivation of HERG channels. Subcellular localization of R863X-EGFP revealed that the mutant did not traffic to the cell surface. These data suggest that R863X failed to form functional HERG channels, contributing to a prolongation of the QT interval and long QT syndrome with a dominant phenotype. These findings provide new insights into the structure-function relationships of the HERG C-terminus.

L4 ANSWER 6 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2005:523695 BIOSIS
DN PREV200510313658
TI A common antitussive drug, clobutinol, precipitates the long-QT2 syndrome.
AU Bellocq, Chloe [Reprint Author]; Wilders, Ronald; Schott, Jean-Jacques; Louerat-Oriou, Benedicte; Boisseau, Pierre; Le Marec, Herve; Escande, Denis; Baro, Isabelle
CS INSERM, U533, Inst Thorax, Nantes, France
SO Circulation, (OCT 26 2004) Vol. 110, No. 17, Suppl. S, pp. 17.
Meeting Info.: 77th Scientific Meeting of the American-Heart-Association. New Orleans, LA, USA. November 07 -10, 2004. Amer Heart Assoc.
CODEN: CIRCAZ. ISSN: 0009-7322.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005
AB QT prolongation, a classical risk factor for arrhythmias can result from a mutation in one of the genes governing cardiac repolarization and also can result from the intake of a medication acting as blocker of the cardiac K+ channel HERG. A 9-year boy diagnosed with congenital long QT2 syndrome (QTc = 597 ms), experienced for the first time torsade-de-pointe arrhythmias while being treated with clobutinol, a commonly used non-opioid antitussive drug. The arrhythmia ceased after the drug was discontinued. In the proband, we identified a novel A561P ***HERG*** ***mutation*** . Both his father and brother are also mutation carrier with a long QT but never experienced syncope or arrhythmia. Two others ***LQT*** mutations (A561V and A561T) had previously been reported at the same position. Neither of the three HERG mutants led to sizeable current in heterologous expression system. When co-expressed with wild-type (WT) HERG channels, the three A561 mutants reduced the trafficking of WT and mutant heteromeric channels resulting in decreased K+ current amplitude (dominant-negative effects). In addition, A561P but not A561V and A561T mutants induced a -11-mV shift in the HERG current activation curve and accelerated deactivation, thereby partially counteracting the dominant-negative effects. Using the patch-clamp technique, we showed that clobutinol dose-dependently inhibited the HERG K+ current with a half-maximum block concentration of 2.9 10(-6) M and a Hill coefficient of 0.9. The effects of the A561P mutation and clobutinol on the human ventricular action potential characteristics were simulated using the Priebe-Beuckelmann computer model. A prolongation of the action potential duration (APD(90)) from 357 to 463 ms (cycle length: 1000 ms) resulted from the A561P ***HERG*** ***mutation*** . Clobutinol, at circulating therapeutic drug concentrations, induced a further APD(90) prolongation from 463 to 503 ms. At the same concentration, clobutinol

prolonged the WT-HERG APD(90) from 357 to 393 ms. Our work shows that a common drug not previously identified as a QT prolonging drug can precipitate the LQT2 syndrome. The drug is not expected to produce clinically relevant effects in individuals with normal cardiac repolarization reserve.

L4 ANSWER 7 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 2003431989 EMBASE
TI [Comparison of Different Formulas of QT Interval Correction in ***LQT*** Families During Exercise].
SROVNANI RUZNYCH METOD KOREKCE QT INTERVALU PRI ZATEZI V RODINACH SE
SYNDROMEM DLOUHEHO QT INTERVALU.
AU Sisakova M.; Vlasinova J.; Semrad B.; Chroust K.; Ravcukova B.
CS Dr. M. Sisakova, Interni Kardiologicka Klinika, FN Brno, Jihlavska 20, 639 00 Brno, Czech Republic
SO Vnitrni Lekarstvi, (2003) Vol. 49, No. 10, pp. 799-801. .
Refs: 13
ISSN: 0042-773X CODEN: VNLEAH
CY Czech Republic
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
LA Czech
SL English; Czech
ED Entered STN: 13 Nov 2003
Last Updated on STN: 13 Nov 2003
AB Background: Pathologic prolongation of QT interval is related to increased risk of arrhythmias. Changes of this parameter are influenced by many conditions, the most important is heart rate. Several formulas have been proposed for mathematical description of QT interval/heart rate relationship. The aim of this study was comparison of different QT interval correction formulas in families with congenital long QT syndrome (LQTS). Methods: In 28 members of 6 families with LQTS occurrence bicycle ergometry testings were performed. QT and RR intervals were measured before exercise, at peak exercise and in the 1st and the 6th minute of restitution. For QT interval correction single-parameter formulas by Bazett, Fridericia, Malik and Framingham study were used. In 3 families the results could be correlated with genetically proved diagnosis (KCNQ1 gene ***mutations*** in 2 families, ***HERG*** -KCNH2 gene ***mutation*** in the other). Results: In the described group the genetically established diagnosis of LQTS correlated at best with values obtained with correction by Bazett. All the mutation carriers were correctly identified only by this method. The Fridericia, Malik and Framingham formulas failed to identify 2 patients - mutation carriers (both KCNQ1 and ***HERG*** -KCNH2 ***mutations***). Discussion: Because of simplicity the Bazett formula remains the most common method of QT interval correction. Moreover, in our study this formula appeared to be the most sensitive for clinical diagnosis of LQTS.

L4 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:562791 CAPLUS
DN 138:100652
TI Pharmacological rescue of human K+ channel long-QT2 mutations: human ether-a-go-go-related gene rescue without block
AU Rajamani, Sridharan; Anderson, Corey L.; Anson, Blake D.; January, Craig T.
CS Department of Medicine (Cardiology), University of Wisconsin, Madison, WI, USA
SO Circulation (2002), 105(24), 2830-2835
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background-Defective protein trafficking is a consequence of gene mutations. Human long-QT (***LQT***) syndrome results from mutations in several genes, including the human ether-a-go-go-related gene (HERG), which encodes a delayed rectifier K+ current. Trafficking-defective mutant HERG protein is a mechanism for reduced delayed rectifier K+ current in LQT2, and high-affinity HERG channel-blocking drugs can result in pharmacol. rescue. Methods and Results-We postulated that drug mols. modified to remove high-affinity HERG block may still stabilize mutant proteins in a conformation required for rescue. The authors tested terfenadine carboxylate (fexofenadine) and terfenadine, structurally similar drugs with markedly different affinities for HERG block, for rescue of trafficking-defective LQT2 mutations. Terfenadine rescued the N470D mutation but blocked the channels. In contrast, fexofenadine rescued N470D with a half-maximal rescue concn. of 177 nmol/L, which is .apprxeq. 350-fold lower than the half-maximal channel block concn. The G601S mutation was also rescued without channel block. Conclusions-Pharmacol. rescue can occur without channel block. This could represent a new antiarrhythmic paradigm in the treatment of some trafficking-defective LQT2 mutations.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:803588 CAPLUS
DN 137:4167
TI Mutation detection in long QT syndrome: A comprehensive set of primers and PCR conditions
AU Syrris, P.; Murray, A.; Carter, N. D.; McKenna, W. M.; Jeffery, S.
CS Medical Genetics Unit, St George's Hospital Medical School, London, SW17 ORE, UK
SO Journal of Medical Genetics (2001), 38(10), 705-710
CODEN: JMDGAE; ISSN: 0022-2593
PB BMJ Publishing Group
DT Journal
LA English
AB A robust and reproducible set of primers was produced for polymerase chain reaction (PCR)/single-strand conformation polymorphism (SSCP) anal. of all five genes involved in the long QT (***LQT***) syndrome. The ext. PCR conditions were defined for a successful amplification of every PCR fragment, which allowed effective mutational anal. of the five known ***LQT*** genes. All KCNQ1 exons were amplified without using formamide, instead, using PCR methods, ***mutation*** screening of ***HERG*** was obtained by amplifying only 19 fragments compared to 20 and 24 by recombining existing primers in a more effective way and then optimizing PCR conditions for each fragment. Four known polymorphisms and two novel changes on KCNQ1 and KCNE1 were obsd. in the evaluation using DNA samples from sudden death cases and controls. In the first gene, two single nucleotide polymorphisms (SNPs) at amino acid positions 546 and 642 and a novel one at position 308 were detected, while a novel SNP and a two known polymorphisms at positions 38 and 85 were detected in KCNE1.
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:98826 CAPLUS
DN 132:162048
TI Mutations in and genomic structure of HERG - a long QT syndrome gene, and ***LQT*** diagnosis
IN Keating, Mark T.; Splawski, Igor
PA University of Utah Research Foundation, USA
SO PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000006772	A1	20000210	WO 1999-US16337	19990720
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6207383	B1	20010327	US 1999-226012	19990106
CA 2336236	AA	20000210	CA 1999-2336236	19990720
AU 9951133	A1	20000221	AU 1999-51133	19990720
AU 774194	B2	20040617		
EP 1102863	A1	20010530	EP 1999-935710	19990720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002521065	T2	20020716	JP 2000-562554	19990720
AU 2004202006	A1	20040610	AU 2004-202006	20040511
PRAI US 1998-122847	A	19980727		
US 1999-226012	A	19990106		
WO 1999-US16337	W	19990720		

AB The invention relates to the detn. of the genomic structure of HERG, a gene assocd. with long QT syndrome, construction of primers for ***mutational*** anal. of ***HERG*** , and newly identified ***mutations*** in ***HERG*** . Methods of diagnosis of mutations causing long QT syndrome using nucleic acid probe hybridization, single stranded conformation polymorphism technique, gene sequencing and amplification, RNAse assay are also described. Also disclosed are methods of diagnosis of long QT syndrome via immunocytochem. technique and immunoblotting with antibodies raised against a mutant HERG polypeptide, and a method of amplifying an exon of HERG using oligonucleotide primers. A method of screening for drugs useful in treating a person with ***mutation*** in ***HERG*** via measurement of a first induced K+ current in cells transformed with HERG and a transgenic animal are also provided. The sequences of the 15 intron/exon junctions has been detd. and this information is useful in devising primers for amplifying and sequencing across all of the exons of the gene. This is useful for detg. the presence or absence of mutations which are known to cause long QT syndrome. Also disclosed are many new ***mutations*** in ***HERG*** which have been found to be assocd. with long QT syndrome. Linkage anal. and phys. and genetic mapping was used to localize HERG to human chromosome 7q35-36 region. Northern blot anal. revealed that HERG is expressed mainly in heart. Combined with sequence homol. data and assocn. of mutation and ***LQT*** , it was suggested that HERG encodes .alpha.-subunit of potassium channel.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 11 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2
AN 2000390094 EMBASE

TI A structural basis for drug-induced long QT syndrome.
AU Mitcheson J.S.; Chen J.; Lin M.; Culberson C.; Sanguinetti M.C.
CS M.C. Sanguinetti, Eccles Institute of Human Genetics, University of Utah, Salt Lake City, UT 84112, United States. mike.sanguinetti@hci.utah.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (24 Oct 2000) Vol. 97, No. 22, pp. 12329-12333. .
Refs: 33
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 13 Dec 2000
Last Updated on STN: 13 Dec 2000
AB ***Mutations*** in the ***HERG*** K+ channel gene cause inherited long QT syndrome (***LQT***), a disorder of cardiac repolarization that predisposes affected individuals to lethal arrhythmias [Curran, M. E., Splawski, I., Timothy, K. W., Vincent, G. M., Green, E. D. and Keating, M. T. (1995) Cell 80, 795-804]. Acquired ***LQT*** is far more common and is most often caused by block of cardiac HERG K+ channels by commonly used medications [Roden, D. M., Lazzara, R., Rosen, M., Schwartz, P. J., Towbin, J. and Vincent, G. M. (1996) Circulation 94, 1996-2012]. It is unclear why so many structurally diverse compounds block HERG channels, but this undesirable side effect now is recognized as a major hurdle in the development of new and safe drugs. Here we use alanine-scanning mutagenesis to determine the structural basis for high-affinity drug block of HERG channels by MK-499, a methanesulfonanilide antiarrhythmic drug. The binding site, corroborated with homology modeling, is comprised of amino acids located on the S6 transmembrane domain (G648, Y652, and F656) and pore helix (T623 and V625)
of the HERG channel subunit that face the cavity of the channel. Other compounds that are structurally unrelated to MK-499, but cause ***LQT*** , also were studied. The antihistamine terfenadine and a gastrointestinal prokinetic drug, cisapride, interact with Y652 and F656, but not with V625. The aromatic residues of the S6 domain that interact with these drugs (Y652 and F656) are unique to eag/erg K+ channels. Other voltage-gated K+ (Kv) channels have Ile and Val (Ile) in the equivalent positions. These findings suggest a possible structural explanation for how so many commonly used medications block HERG but not other Kv channels
and should facilitate the rational design of drugs devoid of HERG channel binding activity.

L4 ANSWER 12 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
STN DUPLICATE 3
AN 2000:452423 BIOSIS
DN PREV200000452423
TI The dominant negative LQT2 mutation A561V reduces wild-type HERG expression.
AU Kagan, Anna; Yu, Zhihui; Fishman, Glenn I.; McDonald, Thomas V. [Reprint author]
CS Section of Molecular Cardiology, Departments of Medicine and Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SO Journal of Biological Chemistry, (April 14, 2000) Vol. 275, No. 15, pp. 11241-11248. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 25 Oct 2000
Last Updated on STN: 10 Jan 2002
AB HERG1 K+ channel mutations are responsible for one form of dominantly inherited long QT syndrome (***LQT***). Some ***LQT*** mutations exert a dominant negative effect on wild-type current expression. To investigate mechanisms of dominant-negative behavior, we co-expressed wild-type HERG with the A561V mutant in mammalian cells. Transfection with various cDNA ratios produced HERG K+ current densities that approached a predicted binomial distribution where mutant and wild-type subunits co-assemble in a tetramer with nearly complete dominance. Using C terminus myc-tagged wild-type HERG we specifically followed the mutant's effect on full-length wild-type HERG protein expression. Co-expression with A561V reduced the abundance of full-length wild-type HERG protein comparable to the current reduction. Reduction of wild-type protein was due to decreased synthesis and increased turnover. Conditions facilitating protein folding (growth at 30 degreeC, or in 10% glycerol) resulted in partial rescue from the dominant effect, as did the 26 S proteosome inhibitor ALLN. Thus, for A561V, dominant negative effects result from assembly of wild-type subunits with mutant very early in production leading to rapid recognition of mutant channels and targeting for proteolysis. These results establish protein misfolding, cellular proofreading, and bystander involvement as contributing mechanisms for dominant effects in LQT2.

L4 ANSWER 13 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4
AN 2000289846 EMBASE
TI Identical twins with long QT syndrome associated with a missense mutation in the S4 region of the HERG.
AU Hayashi K.; Shimizu M.; Ino H.; Okeie K.; Yamaguchi M.; Yasuda T.; Fujino N.; Fuj II H.; Fujita S.; Mabuchi H.
CS Dr. K. Hayashi, Second Department Internal Medicine, School of Medicine, Kanazawa University, Takara-machi 13-1, Kanazawa 920-8640, Japan
SO Japanese Heart Journal, (2000) Vol. 41, No. 3, pp. 399-404. .
Refs: 20
ISSN: 0021-4868 CODEN: JHEJAR
CY Japan
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 7 Sep 2000
Last Updated on STN: 7 Sep 2000
AB Familial long QT syndrome (LQTS) is caused by mutations in genes encoding ion channels important in determining ventricular repolarization. Mutations in at least five genes have been associated with the LQTS. Fire genes, KCNQ1, HERG, SCN5A, KCNE1, and KCNE2, have been identified. We
have identified a missense ***mutation*** in the ***HERG*** gene in identical twins in a Japanese family with LQTS. The identical twins in our study had QT prolongation and the same missense mutation. However only the proband had a history of syncope. Although many mutations in ***LQT*** genes have been reported, there are few reports of twins with LQTS. This is the first report, to our knowledge, of identical twins with a ***HERG*** gene ***mutation*** .

L4 ANSWER 14 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
STN
AN 2000:530282 BIOSIS
DN PREV200000530282
TI Notched T-waves on Holter recordings in long-QT syndrome: A phenotypic marker of ***HERG*** missense ***mutation*** carriers.
AU Lupoglazoff, J. M. [Reprint author]; Denjoy, I.; Berthet, M.; Hainque, B.; Villain, E.; Vaksmann, G.; Klug, D.; Lucet, V.; Coumel, P.; Guicheney, P.
CS Pediatric Cardiology Dept., Robert Debre Hospital, Paris, France
SO European Heart Journal, (August-September, 2000) Vol. 21, No. Abstract Supplement, pp. 353. print.
Meeting Info.: XXII Congress of the European Society of Cardiology. Amsterdam, Netherlands. August 26-30, 2000. European Society of Cardiology.
CODEN: EHJODF. ISSN: 0195-668X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 6 Dec 2000
Last Updated on STN: 11 Jan 2002

L4 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:286083 CAPLUS
DN 130:307553
TI Cloning and expression of human Herg-2 and Herg-3 genes
IN Ganetzky, Barry S.; Titus, Steven A.
PA Wisconsin Alumni Research Foundation, USA
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920760	A2	19990429	WO 1998-US22286	19981021
WO 9920760	A3	19990708		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 5986081	A	19991116	US 1997-956242	19971022
AU 9911108	A1	19990510	AU 1999-11108	19981021
US 6087488	A	20000711	US 1999-351215	19990712
PRAI US 1997-956242	A	19971022		
WO 1998-US22286	W	19981021		

AB This invention provides protein and cDNA sequences for newly identified Herg-2 and Herg-3 genes, which encode polypeptides believed to be of the human ERG ion-channel family. The proteins of the invention have approx. 85% homol. to the known human ERG potassium channel. Said cDNAs and proteins are of interest because ***mutations*** to the ***Herg*** gene can cause long-QT (***LQT***) syndrome, a relatively rare disorder that causes syncope and sudden death due to ventricular arrhythmia.

L4 ANSWER 16 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 5
AN 1999377572 EMBASE
TI Correction of defective protein trafficking of a mutant HERG potassium channel in human long QT syndrome. Pharmacological and temperature effects.

AU Zhou Z.; Gong Q.; January C.T.
CS Z. Zhou, Section of Cardiology, Univ. of Wisconsin Hospitals/Clinics, 600 Highland Ave., Madison, WI 53792, United States. zhz@medicine.wisc.edu
SO Journal of Biological Chemistry, (29 Oct 1999) Vol. 274, No. 44, pp. 31123-31126. .
Refs: 29
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 18 Nov 1999
Last Updated on STN: 18 Nov 1999
AB The chromosome 7-linked form of congenital long QT syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (HERG) that encodes the rapidly activating delayed rectifier potassium channel. One mechanism for the loss of normal channel function in LQT2 is defective protein trafficking, which results in the failure of the channel protein to reach the plasma membrane. Here we show that the N470D LQT2 mutant protein is trafficking-deficient when expressed at 37 .degree.C in HEK293 cells, whereas at 27 .degree.C its trafficking to the plasma membrane and channel function are markedly improved. We further show that the antiarrhythmic drug E-4031, which selectively blocks HERG channels, also corrects defective protein trafficking of the N470D mutant and can restore the generation of HERG current. Similar findings were obtained with the drugs astemizole and cisapride, as well as with high concentrations of glycerol. The effect of E-4031 on HERG protein trafficking was concentration-dependent and required low drug concentrations (saturation present at 5 .mu.M), developed rapidly with drug exposure, and occurred post-translationally. These findings suggest that protein misfolding leading to defective trafficking of some ***HERG*** ***LQT*** ***mutations*** may be corrected by specific pharmacological strategies.

L4 ANSWER 17 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 6
AN 1999108177 EMBASE
TI C-terminal ***HERG*** ***mutations*** : The role of hypokalemia and a KCNQ1- associated mutation in cardiac event occurrence.
AU Berthet M.; Denjoy I.; Donger C.; Demay L.; Hammoude H.; Klug D.; Schulze-Bahr E.; Richard P.; Funke H.; Schwartz K.; Cournel P.; Hainque B.; Guicheney P.
CS Dr. P. Guicheney, INSERM U153, Groupe Hospitalier Pitie-Salpetriere, 47 boulevard de l'Hopital, 75651 Paris Cedex 13, France. pguichen@myologie.infobiogen.fr
SO Circulation, (23 Mar 1999) Vol. 99, No. 11, pp. 1464-1470. .
Refs: 31
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 28 Apr 1999
Last Updated on STN: 28 Apr 1999
AB Background - The long-QT syndrome (LQTS) is a genetically heterogeneous disease in which 4 genes encoding ion-channel subunits have been identified. Most of the mutations have been determined in the transmembrane domains of the cardiac potassium channel genes KCNQ1 and HERG. In this study, we investigated the 3' part of ***HERG*** for ***mutations*** . Methods and Results - New specific primers allowed the amplification of the 3' part of HERG, the identification of 2 missense mutations, S818L and V822 M, in the putative cyclic nucleotide binding domain, and a 1-bp insertion, 3108+ 1G. Hypokalemia was a triggering factor for torsade de pointes in 2 of the probands of these families. Lastly, in a large family, a maternally inherited G to A transition was found in the splicing donor consensus site of HERG, 2592+ 1G-A, and a paternally inherited mutation, A341E, was identified in KCNQ1. The 2 more severely affected sisters bore both mutations. Conclusions - The discovery of mutations in the C-terminal part of HERG emphasizes that this region plays a significant role in cardiac repolarization. Clinical data suggests that these mutations may be less malignant than mutations occurring in the pore region, but they can become clinically significant in cases of hypokalemia. The first description of 2 patients with double heterozygosity associated with a dramatic malignant phenotype implies that genetic analysis of severely affected young patients should include an investigation for >1 mutation in the ***LQT*** genes.

L4 ANSWER 18 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 1999:172172 BIOSIS
DN PREV199900172172
TI Homozygous deletion in KVLQT1 associated with Jervell and Lange-Nielsen syndrome.
AU Chen, Qiuyun; Zhang, Danmei; Gingell, Robert L.; Moss, Arthur J.; Napolitano, Carlo; Priori, Silvia G.; Schwartz, Peter J.; Kehoe, Eileen; Robinson, Jennifer L.; Schulze-Bahr, Eric; Wang, Qing; Towbin, Jeffrey A. [Reprint author]
CS Department of Pediatrics (Cardiology), Baylor College of Medicine, One Baylor Plaza, Room 333E, Houston, TX, 77030, USA
SO Circulation, (March 16, 1999) Vol. 99, No. 10, pp. 1344-1347. print.
CODEN: CIRCAZ. ISSN: 0009-7322.
DT Article
LA English
ED Entered STN: 5 May 1999
Last Updated on STN: 5 May 1999
AB Background-Long-QT (***LQT***) syndrome is a cardiac disorder that causes syncope, seizures, and sudden death from ventricular arrhythmias, specifically torsade de pointes. Both autosomal dominant ***LQT*** (Romano-Ward syndrome) and autosomal recessive ***LQT*** (Jervell and Lange-Nielsen syndrome, JLNS) have been reported. Heterozygous mutations in 3 potassium channel genes, KVLQT1, KCNE1 (minK), and HERG, and the cardiac sodium channel gene SCN5A cause autosomal dominant ***LQT*** . Autosomal recessive ***LQT*** , which is associated with deafness, has been found to occur with homozygous mutations in KVLQT1 and KCNE1 in JLNS
families in which QTc prolongation was inherited as a dominant trait. Methods and Results-An Amish family with clinical evidence of JLNS was analyzed for mutations by use of single-strand conformation polymorphism and DNA sequencing analyses for mutations in all known ***LQT*** genes. A novel homozygous 2-bp deletion in the S2 transmembrane segment of KVLQT1 was identified in affected members of this Amish family in which both QTc prolongation and deafness were inherited as recessive traits. This deletion represents a new JLNS-associated mutation in KVLQT1 and has deleterious effects on the KVLQT1 potassium channel, causing a frameshift and the truncation of the KVLQT1 protein. In contrast to previous reports in which ***LQT*** was inherited as a clear dominant trait, 2 parents in the JLNS family described here have normal QTc intervals (0.43 and 0.44 seconds, respectively). Conclusions-A novel homozygous KVLQT1 mutation causes JLNS in an Amish family with deafness that is inherited as an autosomal recessive trait.

L4 ANSWER 19 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 1999:186447 BIOSIS
DN PREV199900186447
TI Dominant mechanisms in ***LQT*** ***mutations*** of ***HERG*** .
AU Kagan, A. [Reprint author]; Qin, D.; Zhen, M.; Fishman, G. I.; McDonald, T. V.
CS Albert Einstein Col. Med., New York, NY, USA
SO Biophysical Journal, (Jan., 1999) Vol. 76, No. 1 PART 2, pp. A417. print.
Meeting Info.: Forty-third Annual Meeting of the Biophysical Society. Baltimore, Maryland, USA. February 13-17, 1999.
CODEN: BIOJAU. ISSN: 0006-3495.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 5 May 1999
Last Updated on STN: 5 May 1999

L4 ANSWER 20 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 7
AN 1999212014 EMBASE
TI Dysfunction of delayed rectifier potassium channels in an inherited cardiac arrhythmia.
AU Sanguinetti M.C.
CS Dr. M.C. Sanguinetti, University of Utah, Eccles Institute of Human Genetics, 15 N 2030 E, Salt Lake City, UT 84112-5330, United States. mike.sanguinetti@hci.utah.edu
SO Annals of the New York Academy of Sciences, (1999) Vol. 868, pp. 406-413. .
Refs: 55
ISSN: 0077-8923 CODEN: ANYAA
CY United States
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 8 Jul 1999
Last Updated on STN: 8 Jul 1999
AB The rapid (I(Kr)) and slow (I(Ks)) delayed rectifier K+ currents are key regulators of cardiac repolarization. HERG encodes the K(r) channel, and KVLQTI and hminK encode subunits that coassemble to form K(s) channels. Mutations in any one of these genes cause Romano-Ward syndrome, an autosomal dominant form of long QT syndrome (***LQT***). ***Mutations*** in KVLQTI and ***HERG*** are the most common cause of ***LQT*** . Not all missense ***mutations*** of ***HERG*** or KVLTQI have the same effect on K+ channel function. Most mutations result in a dominant-negative effect, but the severity of the resulting phenotype varies widely, as judged by reduction of current induced by coexpression of wild-type and mutant subunits in heterologous expression systems. Mutations in hminK (S74L, D76N) reduce I(Ks) by shifting the voltage dependence of activation and accelerating channel deactivation. A recessive form of ***LQT*** is caused by mutations in either KVLTQI or

hminK. The functional consequences of mutations in delayed rectifier K+ channel subunits are delayed cardiac repolarization, lengthened QT interval, and an increased risk of torsade de pointes and sudden death.

L4 ANSWER 21 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 1999:187485 BIOSIS
DN PREV199900187485
TI Multiple mechanisms of HERG current suppression in LQT2.
AU Hiraoka, M. [Reprint author]; Nakajima, T. [Reprint author]; Furukawa, T. [Reprint author]; Katayama, Y. [Reprint author]; Tanaka, T.; Itoh, T.; Nagai, R.; Sakurada, H.; Nakamura, Y.
CS Medical Research Institute, Tokyo Med and Dent Univ, Tokyo, Japan
SO Biophysical Journal, (Jan., 1999) Vol. 76, No. 1 PART 2, pp. A75. print. Meeting Info.: Forty-third Annual Meeting of the Biophysical Society. Baltimore, Maryland, USA. February 13-17, 1999. CODEN: BIOJAU. ISSN: 0006-3495.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 5 May 1999
Last Updated on STN: 5 May 1999

L4 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:203136 CAPLUS
DN 131:68710
TI Identification of a novel ***HERG*** gene ***mutation*** by PCR-SSCP and cloning analyses
AU Yang, Ping; Armstrong, Martin; Dai, Dezai; Paulussen, Aimee; Luyten, Walter
CS Research Division of Pharmacology, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SO Zhongguo Yaoke Daxue Xuebao (1999), 30(1), 66-68
CODEN: ZHYXE9; ISSN: 1000-5048
PB Zhongguo Yaoke Daxue
DT Journal
LA English
AB To investigate genetic risk factor of Long QT Syndrome (LQTS), ***mutations*** of ***HERG*** gene were screened in individuals susceptible to ***LQT*** and healthy controls by PCR based SSCP anal. A PCR based cloning assay was also developed and used to identify the mutation. An abnormal conformer was found in one healthy control by SSCP screening. This mutation was not able to be identified by direct sequencing. To sep. the mutated allele, the authors transformed it into plasmid and the final sequencing suggested it is a heterozygous 9 base pairs insertion at position 752 of HERG cDNA sequence (5'.fwdarw.3'). This mutation results in a Gly-Ala-Gly insertion in amino acid sequence. Unlike other mutations previously reported, the nine base pairs insertion is not a genetic risk factor of LQTS.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 8
AN 1999071874 EMBASE
TI N-linked glycosylation sites determine HERG: Channel surface membrane expression.
AU Petrecca K.; Atanasiu R.; Akhavan A.; Shrier A.
CS A. Shrier, Department of Physiology, McGill University, 3655 Drummond Street, Montreal, Que. H3G 1Y6, Canada. ashrier@physio.mcgill.ca
SO Journal of Physiology, (15 Feb 1999) Vol. 515, No. 1, pp. 41-48. .
Refs: 26
ISSN: 0022-3751 CODEN: JPHYA7
CY United Kingdom
DT Journal; Article
FS 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 11 Mar 1999
Last Updated on STN: 11 Mar 1999
AB 1. Long QT syndrome (***LQT***) is an electrophysiological disorder that can lead to sudden death from cardiac arrhythmias. One form of ***LQT*** has been attributed to mutations in the human ether-a-go-go-related gene (HERG) that encodes a voltage-gated cardiac K+ channel. While a recent report indicates that ***LQT*** in some patients is associated with a ***mutation*** of ***HERG*** at a consensus extracellular N-linked glycosylation site (N629), earlier studies failed to identify a role for N-linked glycosylation in the functional expression of voltage-gated K+ channels. In this study we used pharmacological agents and site-directed mutagenesis to assess the contribution of N-linked glycosylation to the surface localization of HERG channels. 2. Tunicamycin, an inhibitor of N-linked glycosylation, blocked normal surface membrane expression of a HERG-green fluorescent protein (GFP) fusion protein (HERG(GFP)) transiently expressed in human embryonic kidney (HEK 293) cells imaged with confocal microscopy. 3. Immunoblot analysis revealed that N-glycosidase F shifted the molecular mass of HERG(GFP) stably expressed in HEK 293 cells, indicating the presence of N-linked carbohydrate moieties. Mutations at each of the two putative extracellular N-linked glycosylation sites (N598Q and N629Q) led to a perinuclear subcellular localization of HERG(GFP) stably expressed in HEK 293 cells, with no surface membrane expression. Furthermore, patch clamp analysis revealed that there was a virtual absence of HERG current in the N-glycosylation mutants. 4. Taken together, these results strongly suggest that N-linked glycosylation is required for surface membrane expression of HERG. These findings may provide insight into a mechanism responsible for LQT2 due to N-linked glycosylation-related ***mutations*** of ***HERG*** .

L4 ANSWER 24 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 9
AN 1998282827 EMBASE
TI HERG channel dysfunction in human long QT syndrome. Intracellular transport and functional defects.
AU Zhou Z.; Gong Q.; Epstein M.L.; January C.T.
CS C.T. January, Dept. of Medicine (Cardiology), Univ. of Wisconsin Hospital/Clinics, 600 Highland Ave., Madison, WI 53792, United States. ctj@medicine.wisc.edu
SO Journal of Biological Chemistry, (14 Aug 1998) Vol. 273, No. 33, pp. 21061-21066. .
Refs: 41
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 17 Sep 1998
Last Updated on STN: 17 Sep 1998
AB ***Mutations*** in ***HERG*** are associated with human chromosome 7-linked congenital long QT (***LQT*** -2) syndrome. We used electrophysiological, biochemical, and immunohistochemical methods to study the molecular mechanisms of HERG channel dysfunction caused by ***LQT*** -2 mutations. Wild type ***HERG*** and ***LQT*** -2 ***mutations*** were studied by stable and transient expression in HEK 293 cells. We found that some mutations (Y611H and V822M) caused defects in biosynthetic processing of HERG channels with the protein retained in the endoplasmic reticulum. Other mutations (1593R and G628S) were processed similarly to wild type ***HERG*** protein, but these ***mutations*** did not produce functional channels. In contrast, the T474I ***mutation*** expressed ***HERG*** current but with altered gating properties. These findings suggest that the loss of HERG channel function in ***LQT*** -2 mutations is caused by multiple mechanisms including abnormal channel processing, the generation of nonfunctional channels, and altered channel gating.

L4 ANSWER 25 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 10
AN 1998272678 EMBASE
TI Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1.
AU Splawski I.; Shen J.; Timothy K.W.; Vincent G.M.; Lehmann M.H.; Keating M.T.
CS M.T. Keating, Eccles Institute of Human Genetics, University of Utah, 15 N 2030 E, Salt Lake City, UT 84112, United States. mark@howard.genetics.utah.edu
SO Genomics, (1 Jul 1998) Vol. 51, No. 1, pp. 86-97. .
Refs: 39
ISSN: 0888-7543 CODEN: GNMCEP
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998
AB Long QT syndrome (***LQT***) is a cardiac disorder causing syncope and sudden death from arrhythmias. ***LQT*** is characterized by prolongation of the QT interval on electrocardiogram, an indication of abnormal cardiac repolarization. ***Mutations*** in KVLQT1, ***HERG*** , SCN5A, and KCNE1, genes encoding cardiac ion channels, cause ***LQT*** . Here, we define the complete genomic structure of three ***LQT*** genes and use this information to identify disease- associated mutations. KVLQT1 is composed of 16 exons and encompasses approximately 400 kb. HERG consists of 16 exons and spans 55 kb. Three exons make up KCNE1. Each intron of these genes contains the invariant GT and AG at the donor and acceptor splice sites, respectively. Intron sequences were used to design primer pairs for the amplification of all exons. Familial and sporadic cases affected by ***mutations*** in KVLQT1, ***HERG*** , and KCNE1 can now be genetically screened to identify individuals at risk of developing this disorder. This work has clinical implications for presymptomatic diagnosis and therapy.

L4 ANSWER 26 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 11
AN 1998111183 EMBASE
TI Genetics, molecular mechanisms and management of long QT syndrome.
AU Wang Q.; Chen Q.; Towbin J.A.

CS Dr. Q. Wang, Dept. of Pediatrics (Cardiology), Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, United States. qwang@bcm.tmc.edu
SO Annals of Medicine, (1998) Vol. 30, No. 1, pp. 58-65. .
Refs: 63
ISSN: 0785-3890 CODEN: ANMDEU
CY United Kingdom
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
037 Drug Literature Index
LA English
SL English
ED Entered STN: 23 Apr 1998
Last Updated on STN: 23 Apr 1998
AB Cardiac arrhythmias cause more than 300,000 sudden deaths each year in the USA alone. Long QT syndrome (***LQT***) is a cardiac disorder that causes sudden death from ventricular tachyarrhythmias, specifically torsade de pointes. Four ***LQT*** genes have been identified: KVLQT1 (LQT1) on chromosome 11p15.5, HERG (LQT2) on chromosome 7q35-36, SCN5A
(LQT3) on chromosome 3p21-24, and MinK (LQT5) on chromosome 21q22. SCN5A
encodes the cardiac sodium channel, and ***LQT*** -causing mutations in SCN5A lead to the generation of a late phase of inactivation-resistant whole-cell inward currents. Mexiletine, a sodium channel blocker, is effective in shortening the QT interval corrected for heart rate (QTc) of patients with SCN5A mutations. HERG encodes the cardiac I(Kr) potassium channel. ***Mutations*** in ***HERG*** act by a dominant-negative mechanism or by a loss-of-function mechanism. Raising the serum potassium concentration can increase outward HERG potassium current and is effective in shortening the QTc of patients with ***HERG*** ***mutations*** . KVLQT1 is a cardiac potassium channel protein that interacts with another small potassium channel MinK to form the cardiac I(Ks) potassium channel. Like ***HERG*** ***mutations*** , ***mutations*** in KVLQT1 and MinK can act by a dominant-negative mechanism or a loss-of-function mechanism. An effective treatment for ***LQT*** patients with KVLQT1 or MinK mutations is expected to be developed based on the functional characterization of the I(Ks) potassium channel. Genetic testing is now available for some patients with ***LQT*** .

L4 ANSWER 27 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
STN
AN 1998:522397 BIOSIS
DN PREV199800522397
TI "Touchdown vectorette-PCR": An efficient method for establishing unknown intronic sequences of ***LQT*** genes.
AU Rubie, C. [Reprint author]; Schulze-Bahr, E. [Reprint author]; Myriam, B.; Wedekind, H. [Reprint author]; Haverkamp, W. [Reprint author]; Moennig, G. [Reprint author]; Mergenthaler, J. [Reprint author]; Borggerefe, M. [Reprint author]; Assmann, G.; Breithardt, G. [Reprint author]; Guicheney, P.; Funke, H.
CS Inst. Arteriosclerosis Res., Muenster, Germany
SO European Heart Journal, (Aug., 1998) Vol. 19, No. ABST. SUPPL., pp. 39. print.
Meeting Info.: XXth Congress of the European Society of Cardiology. Vienna, Austria. August 22-26, 1998. European Society of Cardiology. CODEN: EHJODF. ISSN: 0195-668X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 22 Dec 1998
Last Updated on STN: 22 Dec 1998

L4 ANSWER 28 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 12
AN 97318052 EMBASE
DN 1997318052
TI Multi-undulant T-U-wave, sinus bradycardia and long QT syndrome: A possible phenotype of mutant genes controlling the inward potassium rectifiers.
AU Shen C.-T.; Wu Y.-C.; Yu S.-S.-T.; Wang N.-K.
CS Dr. C.-T. Shen, Cathay General Hospital, Jen-Ai Road, Taipei, Taiwan,Province of China. ctsf0901@tpts5.seed.net.tw
SO Acta Paediatrica Sinica, (1997) Vol. 38, No. 4, pp. 267-275. .
Refs: 24
ISSN: 0001-6578 CODEN: CHEKAL
CY Taiwan,Province of China
DT Journal; Article
FS 007 Pediatrics and Pediatric Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 13 Nov 1997
Last Updated on STN: 13 Nov 1997
AB Inward rectifying potassium currents (Ikr and Iks) during phase 3 repolarization of the myocyte from the beginning to the end of repolarization of the myocardial syncytium will inscribe a T-U-wave on the surface electrocardiogram (ECG). Type two congenital long QT syndrome (LQT2) is a phenotype of human ether-a-go-go-related gene (***HERG***) ***mutation*** on the chromosome 7q 35-36. Type one congenital long QT syndrome (LQT1) is a phenotype of KvLQT1 mutation on the chromosome 11p15.5. Both LQT1 and LQT2 relate with inward rectifying potassium currents and is repolarization related, therefore, it is speculate that patients of LQT1 and LQT2 may have an abnormal T-U-wave on their surface ECG. To two probands of congenital ***LQT*** , 8 patients of structural heart disease treated by open heart surgery, 13 patients of structural heart disease without open-heart surgery, and 10 patients of normal controls, 24 hour-Holter monitoring was performed from July to December 1996. Their corrected QT interval (QTc) as well as the RR interval of every heart beat was calculated by a computer. The results showed that all 33 patients exhibited beat-by-beat fluctuation of their QTc and RR daily. The RR intervals of these two probands of congenital ***LQT*** were somewhile more than 1200 ms during circadian waking time, while 31 cases without ***LQT*** showed their RR prolongation only during the circadian sleeping time. A multi-undulant T-U-wave, or a beat-to-beat changing of vectors or amplitudes of their T-U-wave observed in these two probands of congenital ***LQT*** , were not observable in those 31 patients without congenital ***LQT*** . Therefore, we concluded that multi-undulant T-U-wave, sinus bradycardia and a longer QTc was a phenotype of the mutated genes which control the inward rectifying potassium currents during phase 3 repolarization.

L4 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:185322 CAPLUS
DN 126:275543
TI Molecular bases for long QT syndrome (***LQT***): mutations in cardiac ion channel genes cause ***LQT***
AU Nakajima, Tadashi; Keneko, Yoshiaki; Nagai, Kaneko
CS Dep. Internal Med. II, Gunma Univ. Sch. Med., Japan
SO Kokyu to Junkan (1997), 45(2), 121-128
CODEN: KOJUA9; ISSN: 0452-3458
PB Igaku Shoin
DT Journal; General Review
LA Japanese
AB A review with 22 refs., on the theory of inherited Long QT syndrome, and genetic factors and abnormal ion channels (i.e. KVLQT1, HERG, and SCN5A) in Romano-Ward syndrome.

L4 ANSWER 30 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 13
AN 96081969 EMBASE
DN 1996081969
TI Spectrum of HERG K+-channel dysfunction in an inherited cardiac arrhythmia.
AU Sanguinetti M.C.; Curran M.E.; Spector P.S.; Keating M.T.
CS EPHMBG, Cardiology Division, Univ. of Utah Health Sciences Center,Salt Lake City, UT 84112, United States
SO Proceedings of the National Academy of Sciences of the United States of America, (1996) Vol. 93, No. 5, pp. 2208-2212. .
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
LA English
SL English
ED Entered STN: 2 Apr 1996
Last Updated on STN: 2 Apr 1996
AB Long QT syndrome (***LQT***) is an autosomal dominant disorder that can cause sudden death from cardiac arrhythmias. We recently discovered that ***mutations*** in ***HERG*** , a K+-channel gene, cause chromosome 7-linked ***LQT*** . Heterologous expression of HERG in Xenopus oocytes revealed that HERG current was similar to a well-characterized cardiac delayed rectifier K+ current, I(Kr), and led to the hypothesis that ***mutations*** in ***HERG*** reduced I(Kr), causing prolonged myocellular action potentials. To define the mechanism of ***LQT*** , we injected oocytes with mutant HERG complementary RNAs, either singly or in combination with wild-type complementary RNA. Some mutations caused loss of function, whereas others caused dominant negative suppression of HERG function. These mutations are predicted to cause a spectrum of diminished I(Kr) and delayed ventricular repolarization, consistent with the prolonged QT interval observed in individuals with ***LQT*** .

L4 ANSWER 31 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 14
AN 96160787 EMBASE
DN 1996160787
TI Missense mutation in the pore region of HERG causes familial long QT syndrome.
AU Benson D.W.; MacRae C.A.; Vesely M.R.; Walsh E.P.; Seidman J.G.; Seidman
C.E.; Satler C.A.
CS Department of Cardiology, Children's Hospital, 300 Longwood Ave,Boston, MA
02115, United States
SO Circulation, (1996) Vol. 93, No. 10, pp. 1791-1795. .
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English

ED Entered STN: 11 Jun 1996
Last Updated on STN: 11 Jun 1996
AB Background. Long QT syndrome (***LQT***) is an inherited cardiac disorder that results in syncope, seizures, and sudden death. In a family with ***LQT*** , we identified a novel mutation in human ether-a-go-go-related gene (HERG), a voltage-gated potassium channel. Methods and Results. We used DNA sequence analysis, restriction enzyme digestion analysis, and allele-specific oligonucleotide hybridization to identify the ***HERG*** ***mutation*** . A single nucleotide substitution of thymidine to guanine (T1961G) changed the coding sense of HERG from isoleucine to arginine (Ile593Arg) in the channel pore region. The mutation was present in all affected family members; the mutation was not present in unaffected family members or in 100 normal, unrelated individuals. Conclusions. We conclude that the Ile593Arg missense ***mutation*** in ***HERG*** is the cause of ***LQT*** in this family because it segregates with disease, its presence was confirmed in three ways, and it is not found in normal individuals. The Ile593Arg mutation may result in a change in potassium selectivity and permeability leading to a loss of HERG function, thereby resulting in ***LQT*** .

L4 ANSWER 32 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 15
AN 96278365 EMBASE
DN 1996278365
TI A ***mutation*** in ***HERG*** associated with notched T waves in long QT syndrome.
AU Dausse E.; Berthet M.; Denjoy I.; Andre-Fouet X.; Cruaud C.; Bennaceur M.; Faure S.; Coumel P.; Schwartz K.; Guicheney P.
CS INSERM UR153, Hopital Pitie-Salpetriere, Institut de Myologie, 47 boulevard de l'Hopital,75013 Paris, France
SO Journal of Molecular and Cellular Cardiology, (1996) Vol. 28, No. 8, pp. 1609-1615. .
ISSN: 0022-2828 CODEN: JMCDAY
CY United Kingdom
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 7 Oct 1996
Last Updated on STN: 7 Oct 1996
AB Long QT syndrome (***LQT***) is a genetically heterogeneous inherited disorder that causes sudden death from cardiac arrhythmia. Four loci have been mapped to chromosomes 3, 4, 7 and 11 and three specific mutated genes for ***LQT*** syndrome have been identified. LQT2 results from mutations in the human ether-a-gogo-related gene, HERG, a cardiac potassium channel, whose protein product likely underlies I(K)r, the rapidly activating delayed rectifier current. By SSCP analysis and direct sequencing, we determined a new missense ***mutation*** in the ***HERG*** coding sequence, a G to A transition at position 1681 resulting in the substitution of threonine for a highly conserved alanine at codon 561. This mutation, Ala561Thr, in the coding sequence of the fifth membrane-spanning domain (S5) of the HERG protein seems to convey a risk of cardiac events in affected family members. In addition to a prolonged T wave of low amplitude on the surface ECG, a distinctive biphasic T-wave pattern was found in the left precordial leads of all affected subjects with the Ala561Thr mutation regardless of age, gender and beta blocking therapy.

L4 ANSWER 33 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 16
AN 96270661 EMBASE
DN 1996270661
TI Genetically defined therapy of inherited long-QT syndrome: Correction of abnormal repolarization by potassium.
AU Compton S.J.; Lux R.L.; Ramsey M.R.; Strelich K.R.; Sanguinetti M.C.; Green L.S.; Keating M.T.; Mason J.W.
CS Division of Cardiology, Univ. of Utah Health Sciences Center,Salt Lake City, UT 84132-0001, United States
SO Circulation, (1996) Vol. 94, No. 5, pp. 1018-1022. .
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
ED Entered STN: 1 Oct 1996
Last Updated on STN: 1 Oct 1996
AB Background: Many members of families with inherited long-QT (***LQT***) syndrome have ***mutations*** in ***HERG*** , a gene encoding a cardiac potassium channel that is modulated by extracellular potassium. We hypothesized that an increase in serum potassium would normalize repolarization in these patients. Methods and Results: We studied seven subjects with chromosome 7-linked ***LQT*** syndrome and five normal control subjects. Repolarization was measured by ECG and body surface potential mapping during sinus rhythm, exercise, and atrial pacing, before and after serum potassium increase. Potassium administration improved repolarization in the ***LQT*** syndrome. At baseline, ***LQT*** subjects differed form control subjects: resting corrected QT interval (QT(c), 627.+-.90 versus 425.+-.25 ms, P=.0007), QT(c) dispersion (133.+-.62 versus 36.+-.9 ms, P=.009), QT/RR slope (0.35.+-.0.08 versus 0.24.+-.0.07, P=.04) and global root- mean-square QT interval (RMS-QT(c); 525.+-.68 versus 393.+-.22, P=.002). All ***LQT*** subjects had biphasic or notched T waves. After administration of potassium, the ***LQT*** group had 24% reduction in resting QT(c) interval (from 617.+-.92 to 469.+-.2.3 ms, P=.004) compared with a 4% reduction among control subjects (from 425.+-.25 to 410.+-.45 ms, P>.05). The reduction was significantly greater in ***LQT*** subjects (P=.018). QT dispersion became normal in ***LQT*** subjects and did not change in control subjects. The slope of the relation between QT interval and cycle length (QT/RR slope) decreased toward normal. T-wave morphology improved in six of seven ***LQT*** subjects. The ***LQT*** group had a greater reduction in RMS-QT(c) than control subjects (P=.04). Conclusions: An increase in serum potassium corrects abnormalities of repolarization duration. T-wave morphology, QT/RR slope, and QT dispersion in patients with chromosome 7- linked ***LQT*** .

L4 ANSWER 34 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 17
AN 95081536 EMBASE
DN 1995081536
TI A molecular basis for cardiac arrhythmia: ***HERG*** ***mutations*** cause long QT syndrome.
AU Curran M.E.; Splawski I.; Timothy K.W.; Vincent G.M.; Green E.D.; Keating M.T.
CS Eccles Program in Human Molec. Biol., Department of Human Genetics, Univ. of Utah Health Sciences Center,Salt Lake City, UT 84112, United States
SO Cell, (1995) Vol. 80, No. 5, pp. 795-803. .
ISSN: 0092-8674 CODEN: CELLB5
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 29 Mar 1995
Last Updated on STN: 29 Mar 1995
AB To identify genes involved in cardiac arrhythmia, we investigated patients with long QT syndrome (***LQT***), an inherited disorder causing sudden death from a ventricular tachyarrhythmia, torsade de pointes. We previously mapped ***LQT*** loci on chromosomes 11 (LOT1), 7 (LQT2), and 3 (LQT3). Here, linkage and physical mapping place LQT2 and a putative potassium channel gene, HERG, on chromosome 7q35-36. Single strand conformation polymorphism and DNA sequence analyses reveal ***HERG*** ***mutations*** in six ***LQT*** families, including two intragenic deletions, one splice-donor mutation, and three missense mutations. In one kindred, the mutation arose de novo. Northern blot analyses show that HERG is strongly expressed in the heart. These data indicate that HERG is LQT2 and suggest a likely cellular mechanism for torsade de pointes.

L4 ANSWER 35 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 18
AN 95143848 EMBASE
DN 1995143848
TI A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I(Kr) potassium channel.
AU Sanguinetti M.C.; Jiang C.; Curran M.E.; Keating M.T.
CS Eccles Human Molecular Biology Prog., Univ. of Utah Health Sciences Center,Salt Lake City, UT 84112, United States
SO Cell, (1995) Vol. 81, No. 2, pp. 299-307. .
ISSN: 0092-8674 CODEN: CELLB5
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 23 May 1995
Last Updated on STN: 23 May 1995
AB ***Mutations*** in ***HERG*** cause an inherited cardiac arrhythmia, long QT syndrome (***LQT***). To define the function of HERG, we expressed the protein in Xenopus oocytes. The biophysical properties of expressed HERG are nearly identical to the rapidly activating delayed rectifier K+ current (I(Kr)) in cardiac myocytes. HERG current is K+ selective, declines with depolarizations above 0 mV, is activated by extracellular K+, and is blocked by lanthanum. Interestingly, HERG current is not blocked by drugs that specifically block I(Kr) in cardiac myocytes. These data indicate that HERG proteins form I(Kr) channels, but that an additional subunit may be required for drug sensitivity. Since block of I(Kr) is a known mechanism for drug-induced cardiac arrhythmias, the finding that HERG encodes I(Kr) channels provides a mechanistic link between certain forms of inherited and acquired ***LQT*** .

L4 ANSWER 36 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 19
AN 95197880 EMBASE
DN 1995197880
TI Genetic approaches to cardiovascular disease: Supravalvular aortic stenosis, Williams syndrome, and long-QT syndrome.
AU Keating M.T.
CS Eccles Institute of Human Genetics, University of Utah, Building 533,Salt

Lake City, UT 84112, United States
SO Circulation, (1995) Vol. 92, No. 1, pp. 142-147. .
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English
SL English
ED Entered STN: 18 Jul 1995
Last Updated on STN: 18 Jul 1995
AB Background: Although family history can be an important risk factor for cardiovascular disease, relatively little is known about the nature of specific genetic risk factors. One approach to this problem is to identify and characterize genes responsible for inherited disorders in the hope that this information will also provide mechanistic insight into common forms of cardiovascular disease. Methods and Results: Over the last decade, it has become possible to identify genes that cause human disease by use of the techniques of molecular genetics, specifically genetic linkage analysis, positional cloning, and mutational analyses. We have used these techniques to study three inherited cardiovascular disorders: supravalvular aortic stenosis, Williams syndrome, and long-QT syndrome. We have discovered that the vascular pathology of supravalvular aortic stenosis and Williams syndrome results from mutations involving the elastin gene on chromosome 7q11.23. These mutations include intragenic deletions, translocations, and complete deletion of the elastin gene, suggesting that a quantitative reduction in elastin during vascular development is pathogenically important. To date, only the elastin gene has proved important for supravalvular aortic stenosis. By contrast, genetic linkage analyses in families with long-QT syndrome indicate that at least four distinct genes can cause this disorder. We have identified three ***LQT*** loci: LQT1 on chromosome 11p15.5, LQ72 on 7q35-36, and LQT3 on 3p21-24. Recently, we demonstrated that mutations in a putative cardiac potassium channel gene, HERG, are responsible for the chromosome 7- linked form of long-QT syndrome, whereas mutations in the cardiac sodium channel gone SCN5A cause the chromosome 3-linked form of this disorder. ***HERG*** ***mutations*** and potassium channel biophysics suggest a dominant-negative molecular mechanism and reduced repolarization currents. By contrast, SCN5A mutations probably cause subtle alterations of cardiac sodium channel function and prolonged alepolarizing currents. Conclusions: Molecular generic analyses of long-QT syndrome, supravalvular aortic stenosis, and Williams syndrome have begun to unravel the mechanisms underlying these inherited disorders. Rapid genetic testing for Williams syndrome is now available using a simple cytogenetic test, fluorescence in situ hybridization, but additional work will be required for long-QT syndrome and autosomal-dominant supravalvular aortic stenosis. Improved diagnosis and mechanistic understanding of these disorders should lead to rational treatment and prevention.

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